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THE BACTERICIDAL AND PROTOZOACIDAL ACTIVITY OF EMETIN HYDROCHLORID IN VIVO *

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Having found that emetin hydrochlorid possesses some bactericidal and trypanocidal power in vitro, as shown in our previous communication,[1] we have investigated the possibility of its exerting similar influence in vivo.

Emetin has been used successfully in the treatment of amebic dysentery by hypodermatic injection from the time of its introduction by Rogers,[2] and the studies of Vedder[5] and others leave no doubt regarding the high specificity and the parasitropic action of ipecac and emetin for amebae. Rogers, it is said, was preceded in the use of emetin in dysentery by Dr. W. S. Eccles in India in 1869,[3] and Harris is said also to have employed the remedy at an early date,[4] at Simla. However, the work of Rogers, independent of these and really based on Vedder's studies, is actually the basis for the modern clinical use of emetin in amebic dysentery and its complications. Bass and Johns[6] have advocated the hypodermatic injection of emetin in the treatment of amebic pyorrhea and, while this form of treatment has not proved in our experience as successful as the local application of emetin, yet there is abundant evidence showing the amebacidal and curative action of this drug when so administered.

In addition to this amebacidal activity of emetin,[7] the improvement of various arthritic, neuritic, digestive, hemic, and other complications of pyorrhea alveolaris (attributed to a condition of toxemia) following the local application and especially the hypodermatic injection of emetin, as reported by Evans and Middleton; the amelioration of symptoms and some improvement in patients with pulmonary tuberculosis under treatment with emetin, as reported by Tatchell;[8] and the value of emetin administered subcutaneously as a form of abortive treatment of typhoid fever, as reported by Frazier[9]—all suggest that emetin may exert some bactericidal action in vivo.

The view generally held by those who have noted the beneficial influence of hypodermatically administered emetin on various complications of amebic dysentery and amebic pyorrhea has been to the effect that the drug was mainly amebacidal and that as a result of the destruction of amebae there was coincident cessation of the formation of amebic and bacterial toxins and

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[1] Jour. Infect. Dis., 1916, 18, p. 247.

[2] Brit. Med. Jour., 1912, 1, p. 1424; 2, p. 405.

[3] Practitioner, 1914, 93, p. 4.

[4] Indian Med. Gaz., 1914, 49, p. 193.

[5] Jour. Am. Med. Assn., 1914, 62, p. 501 (full bibliography to literature).

[6] Ibid., 1915, 64, p. 553.

[7] Ibid., p. 422.

[8] China Med. Jour., 1915, 29, p. 167.

[9] Med. Rec., 1915, 87, p. 476.

of the mechanical conveyance of bacteria into deeper tissues. Smith and Barrett[10] believe that the amebae act in symbiotic relation with some or all of the micro-organisms with which they are associated in nature, and that the amebae by their digestive processes not only furnish a highly fitting pabulum for the growth of these bacteria but aid in setting free bacterial toxins which cause local necrosis and may be productive of a widespread series of complications. The destruction of amebae would be followed therefore by diminished toxin-production, by the removal of a source of food supply for bacteria, and by the loss of a means of their mechanical conveyance into deeper tissues through the migratory habits of the amebae.

SCOPE OF THIS INVESTIGATION

We have studied the bactericidal action of emetin in vivo on Staphylococcus aureus, Bacillus tetanus, and Bacillus anthracis. These bacteria were selected because of the ease with which the lethal dose of each may be determined, the certainty of their pathogenicity for experimental animals, and the relatively high bactericidal action of emetin in vitro on spore-forming bacteria.

The trypanocidal activity of emetin in vivo was studied with Trypanosoma equiperdum and T. lewisi. The amebacidal action of emetin was of minor importance in this investigation by reason of the large amount of work that had been done in this direction and the unanimous weight of opinion regarding the highly specific amebacidal action of ipecac and emetin.

In studying the influence of emetin on Staphylococcus aureus in vivo, rabbits were used; for B. tetanus and B. anthracis, white mice were employed; and for T. equiperdum and T. lewisi, white rats.

THE LETHAL DOSE OF EMETIN

In many of our experiments emetin was administered intravenously, and in all instances the doses were based on the weight of the animal (rabbits, mice, and rats), being so graded that each animal received a certain quantity per 60 kilos of body-weight (about 132 pounds, adopted as an average weight for adult human beings).

By intravenous injection the immediate lethal dose of emetin for white rats was found to be about 0.016 gm. (¼ grain) per kilo of body-weight, which is equivalent to 0.96 gm. (about 15 grains) per 60 kilos (132 pounds). In this animal a dose equivalent to 1.17 and 1.3 gm. (18 and 20 grains) per 60 kilos of body-weight was invariably fatal, while most animals withstood a dose equivalent to 0.77 gm. (12 grains) or 0.0129 gm. per kilo (equivalent to about ⅕ grain per kilo).

Emetin was found slightly more toxic for rabbits. A dose equivalent to from 0.77 to 0.96 gm. (12 to 15 grains) per 60 kilos of weight (.013 gm. or ⅕ to .016 gm. or ¼ grain per kilo) was usually immediately fatal on intravenous injection; one rabbit succumbed to a dose equivalent to 0.51 gm. (8 grains) per 60 kilo of weight (equivalent to about .009 gm. or 1/7 grain per kilo). In our experiments the immediate lethal dose of emetin for rabbits was from 0.65 gm. to 0.78 gm. (10 to 12 grains) per 60 kilos, which are equivalent to 0.01 to 0.0129 gm., (about 1/6 to 1/5 grain) per kilo.

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[10] Oral Health, 1915, 5, p. 137.

As emetin hydrochlorid is usually administered to man by subcutaneous injections in doses of from 0.016 gm. to 0.065 gm. (1/4 to 1 grain), it is relatively free of organotropic action in so far at least as immediately harmful effects are concerned.

BACTERICIDAL ACTION OF EMETIN HYDROCHLORID IN VIVO

On Staphylococcus aureus.—In our first experiments rabbits were given an intravenous injection of 1 c.c. of a 24-hour broth culture of virulent Staphylococcus aureus—filtered through sterile filter paper to remove large clumps of the cocci. Two hours later emetin, dissolved in sterile normal salt solution, was administered in varying doses by intravenous injection to all animals except the controls. Three to five days later the animals were chloroformed and examined macroscopically and microscopically for staphylococcus abscesses in the kidneys, heart, peritoneum, etc.

In Table 1 are shown the results of this experiment:

TABLE 1

The Action of Emetin on Staphylococcus aureus in Vivo

Rabbit	Weight (Grams)	Dose of Emetin* (Grams)	Equivalent in Grains per 60 K. (or 132 lb.) Body Weight	General Condition	Died	Autopsy 3 Days Later
1	1317	.0559	4	Good	......	Abscesses in kidneys, heart, etc.
2	1580	.005	3	Good	......	Abscesses in kidneys, heart, etc.
3	1255	.00256	2	Good	......	A few microscopic abscesses in one kidney
4	1370	.00146	1	Good	......	A few microscopic abscesses in both kidneys
5	1178	Control	0	Good	3rd day	Abscesses in kidneys, heart, pleura, etc.
6	1258	Control	0	Poor	......	Abscesses in heart, kidneys, pleura, etc.

* Single dose 2 hours after infection.

They may be considered generally of a negative character. One noticeable feature was the evident toxemia of the controls as compared to the well-being of the animals receiving emetin. Whether or not the absence of macroscopic abscesses in the organs of Rabbits 2 and 4 may be attributed to some bactericidal action of emetin is difficult to state. Since microscopic abscesses were found, we are inclined to ascribe the results to a higher resistance on the part of these animals to the cocci.

In order to test this conclusion by a more delicate experiment, a second series of rabbits was given emetin intravenously immediately before the injection of staphylococci, and the same dose repeated at daily intervals for 3 doses, also by intravenous injection. In this experiment the same culture of Staphylococcus aureus was used, but the infecting dose was made 0.5 c.c. of a filtered 24-hour broth culture, instead of 1 c.c. as used in the preceding experiment.

The results are shown in Table 2:

TABLE 2

THE ACTION OF EMETIN ON STAPHYLOCOCCUS AUREUS IN VIVO (MULTIPLE DOSES OF EMETIN)

Rabbit	Weight (Grams)	Dose of Emetin (Grams)	Equivalent in Grains per 60 K. (or 132 lb.) Body Weight	Number of Doses	Total Amount of Emetin Administered	General Condition	Died	Autopsy 5 Days After Infection
1	1147	.0097	8	1	......	......	Immediately	Lethal dose of emetin
2	1354	.0057	4	4	.0228	Slightly toxic	......	A few abscesses in kidneys
3	1084	.0023	2	4	.0092	Good	......	Abscesses in kidneys and heart
4	1211	.0013	1	4	.0052	Good	......	Abscesses in kidneys and heart
5	1000	Control	....	......	......	Fair	......	Abscesses in kidneys, heart, etc.
6	1034	Control	....	......	......	Fair	......	Abscesses in heart, kidneys, etc.

With these results after the daily administration of relatively large doses of emetin by intravenous injection, and with an infection as light as was consistent with constant effects, we must conclude that emetin possesses slight, if any, bactericidal effect in vivo on virulent staphylococci.

On Bacillus anthracis.—A culture of B. anthracis was cultivated in neutral broth for 24 hours, shaken briefly with sterile glass beads, and its lethal dose in 24 hours determined by injecting a series of white mice subcutaneously with amounts varying from 0.001 to 0.4 c.c. With this culture 0.05 c.c. proved fatal with regularity at the expiration of about 24 hours.

A series of mice was then infected with 0.1 c.c., or double the 24-hour lethal dose of anthrax culture, by subcutaneous injection; 2 hours later emetin was administered by intraperitoneal injection. The results are shown in Table 3. They suggest that the deaths of Mice 1 and 2 were hastened by the large doses of emetin, that there was some slight bactericidal effect in Mice 3 and 4, and that the smaller doses exerted no influence (Mice 5, 6, and 7).

TABLE 3

ACTION OF EMETIN ON B. ANTHRACIS

Mouse	Weight (Grams)	Dose* of Emetin (Grams)	Equivalent in Grains per 60 K. or 132 lb. Body Weight	Day of Death		
				1	2	3
1	25	.000267	10	+		
2	22	.000188	8	+		
3	21	.000128	6	—	+	
4	15	.000064	4	—	+	+
5	18	.000057	3	+		
6	19	.0000428	2	+		
7	18	.0000192	1	+		
8	20	Control	..	+		
9	25	Control	..	+		
10	22	Control	..	+		

* Single dose 2 hours after infection.

All these animals showed enormous numbers of anthrax bacilli in the capillaries of the liver, kidney, heart, etc.

This experiment was then repeated; a smaller infecting dose of a 24-hour broth culture of B. anthracis (0.05 c.c.) was subcutaneously injected, and emetin was administered intraperitoneally immediately before injecting the bacilli and again at daily intervals until the mice succumbed. After death autopsies were performed and the internal organs fixed, cut, and stained for anthrax bacilli. The results are shown in Table 4.

TABLE 4

ACTION OF EMETIN ON B. ANTHRACIS (MULTIPLE DOSES OF EMETIN)

Mouse	Weight (Grams)	Dose of Emetin (Grams)	Equivalent in Grains per 60 K. or 132 lb. Body Weight	Total Amount of Emetin Administered	Number of Doses	Day of Death			
						1	2	3	4
1	25	.000321	12	.000641	2	—	+		
2	20	.000214	10	.000642	3	—	—	+	
3	18	.000153	18	.000659	3	—	—	+	
4	19	.000122	16	.000244	2	—	+		
5	21	.0000856	4	.000171	2	—	+		
6	18	.0000385	2	.000115	3	—	—	+	
7	17	.0000181	1	.000072	4	—	—	—	+
8	22	Control	..	....	..	—	—	+	
9	24	Control	..	....	..	—	+		
10	18	Control	..	....	..	—	—	+	

According to these experiments we cannot ascribe to emetin any decided bactericidal value in vivo on the anthrax bacillus; altho it would appear in this experiment and in that shown in Table 3 that when emetin is administered in very large doses slight antiseptic rather than true germicidal effects may be noted.

On Bacillus tetanus.—In working with the tetanus bacillus there was difficulty in infecting the animals with a lethal dose of the bacilli and spores which would be free as possible from preformed toxin. It was not reasonable to expect emetin to be antitoxic, and an excess of toxin might be expected to kill the animals without determining any possible influence of the drug on the bacilli and spores alone.

Neutralization of broth cultures of tetanus bacilli with antitoxin and separation of the bacilli by centrifugation did not yield satisfactory and constant results. After several preliminary trials with an anaerobic culture of the bacillus in a large tube of agar agar, we succeeded in determining the lethal dose by subcutaneous injection of an emulsion prepared with definite volume of the agar culture in 5 c.c. of sterile, neutral broth. Having determined the lethal dose for a 48-hour period, a series of white mice was infected by subcutaneous injection with double this dose, followed 1 hour later by increasing doses of emetin administered by intraperitoneal injection. The results of this experiment are shown in Table 5:

TABLE 5

Action of Emetin on B. Tetanus

Mouse	Weight (Grams)	Dose* of Emetin (Grams)	Equivalent in Grains per 60 K. or 132 lb. Body Weight	Day of Death	
				1	2
1	20	.000171	8	—	+
2	22	.000141	6	—	+
3	24	.000128	5	—	+
4	25	.0000107	4	—	+
5	25	.0000802	3	—	+
6	22	.000047	2	—	+
7	19	.00002	1	—	+
8	22	Control	...	—	+
9	20	Control	...	—	+
10	18	Control	...	—	+

* Single dose 1 hour after infection.

This experiment was then repeated by infecting a series of mice with a dose of bacillus emulsion that in preliminary experiments had proved regularly fatal 3 days after subcutaneous injection. Emetin was administered by intraperitoneal injection immediately before the injection of bacilli and subsequently at daily intervals until the animals succumbed. The results are shown in Table 6.

TABLE 6

ACTION OF EMETIN ON B. TETANUS (MULTIPLE DOSES OF EMETIN)

Mouse	Weight (Grams)	Dose of Emetin (Grams)	Equivalent in Grains per 60 K. or 132 lb. Body Weight	Number of Doses	Total Amount of Emetin Administered	Day of Death		
						1	2	3
1	20	.000381	15	2	.000762	—	+	
2	25	.000321	12	3	.000963	—	—	+
3	18	.000193	10	2	.000386	—	+	
4	17	.000145	8	2	.000290	—	+	
5	22	.00014	6	2	.00028	—	+	
6	24	.000102	4	3	.000306	—	—	+
7	25	.000054	2	3	.000152	—	—	+
8	20	.000021	11	3	.000063	—	—	+
9	18	Control	..	...	....	—	—	+
10	16	Control	..	...	....	—	—	+

In both experiments all the mice showed the characteristic symptoms of tetanus intoxication before succumbing. In the second experiment the death of several mice before the death of the controls may have been due in part to the toxic action of emetin.

In view of these results with relatively large doses of emetin we may conclude that the drug exerted no appreciable bactericidal action in vivo on the tetanus bacillus. We must state, however, that some soluble and preformed toxin may have been present, and probably was, so that the slight bactericidal action of emetin in vivo, as shown with the anthrax bacillus was overshadowed by it in the experiments with tetanus bacilli.

TRYPANOCIDAL ACTION OF EMETIN HYDROCHLORID IN VIVO

On Trypanosoma equiperdum.—In these experiments white rats were infected with trypanosomes by intraperitoneal injections of approximately known numbers after the method of Kolmer.[11] Twenty-four hours later emetin, dissolved in sterile salt solution, was administered intravenously in increasing doses according to body-weight. The rats were examined daily for trypanosomes in the peripheral blood; in this manner we hoped to detect any trypanocidal action which emetin might exert in vivo.

The strain of T. equiperdum employed kills white rats with regularity from 4 to 6 days after infection with the dose employed. In this manner the duration of life alone could be accepted as a criterion of trypanocidal influence among those rats receiving emetin.

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[11] Jour. Infect. Dis., 1915, 16, p. 311; 17, p. 79.

The results of these experiments are shown in Table 7. The first 4 rats died within a few minutes after the injection had been made, as the result of the toxicity of the very large dose of emetin. In a general way it would appear that emetin had exerted a slight trypanocidal action in vivo—shown in Rat 6, which remained sterile for 12 days, and in the slight lengthening of the duration of life in Rats 5, 11, 12, 13, and 15.

Rat 6 had received a dose equivalent to 0.65 gm. (10 grains) for a 132-pound man, which was but slightly under the lethal dose for this animal; likewise, the remaining animals had received relatively large doses, so that we may state that the trypanocidal action of emetin in vivo is very slight, and in evidence only when the drug is given in large doses.

On Trypanosoma lewisi.—Somewhat similar results were observed in our experiments with T. lewisi. These were conducted in exactly the same manner as were the experiments just described. The results of one experiment are shown in Table 8.

The strain of T. lewisi used was slightly pathogenic, in that infected rats begin to die off about 20 days after infection with the dose employed in our experiments. In this series the animals died at very irregular intervals and among the animals receiving emetin no influence on the duration of life was apparent. It is probable that the life of Rat 1 was shortened by the large dose of emetin administered.

The trypanocidal influence of emetin in vivo, if the drug really possesses this action, is very slight indeed; in this experiment it was shown by only a slight retardation of the multiplication of trypanosomes in the peripheral blood.

AMEBACIDAL ACTION OF EMETIN HYDROCHLORID IN VIVO

Our experience with emetin on amebae in vivo is limited to the use of the drug, administered hypodermatically, in the treatment of amebic pyorrhea. Bass and Johns[12] were the first to advocate this form of treatment, reporting that with the subcutaneous injection of 0.032 gm. of emetin daily for from 1 to 3 doses endamebae disappeared from all lesions in the mouth in more than 90% of all cases. After 6 treatments they disappeared in 99% of cases.

While in our experience the endamebae are best attacked by the local use of emetin, we have noted the amebacidal action of the drug administered hypodermatically; similar reports have been made by others and when it is considered that even a dose of 0.016 to 0.065 gm.

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[12] New Orleans Med. and Surg. Jour., 1914, 67, p. 456. Jour. Am. Med. Assn., 1915, 64, p. 553.

TABLE 7

ACTION OF EMETIN HYDROCHLORID IN VIVO ON T. EQUIPERDUM *

Rat	Weight (Grams)	Dose of Emetin (Grams)	Equivalent in Grains per 60 K. or 132 lb. Body Weight	Results of Examination of Blood from Tail											
				24 Hr.	48 Hr.	72 Hr.	96 Hr.	5 Da.	6 Da.	7 Da.	8 Da.	9 Da.	10 Da.	11 Da.	12 Da.
1	101	.00428	40	Died at once											
2	80	.00342	40	Died at once											
3	72	.00154	20	Died at once											
4	98	.00212	20	Died at once											
5	98	.00107	10	—	Few	+	++	++++	++++	Died					
6	98	.00107	10	—	—	—	—	—	Few	Few	++	++++	++++	++++	Died
7	100	.000856	8	—	Few	++	+++	Died							
8	92	.000787	8	—	Few	Died									
9	96	.000616	6	—	Few	++	+++	++++	Died						
10	103	.00063	6	—	Died										
11	96	.00041	4	—	Few	+++	++++	++++	++++	Died					
12	87	.00037	4	—	Few	+++	++++	++++	++++	Died					
13	70	.000149	2	—	Few	++	++++	++++	++++	Died					
14	78	.000166	2	—	Few	+++	++++	Died							
15	80	.000085	1	—	Few	++	+++	++++	++++	Died					
16	83	.000088	1	—	Few	++	Died								
17	80	Control	..	—	Few	+++	++++	Died							
18	100	Control	..	—	+	++++	++++	Died							
19	92	Control	..	—	+	++++	Died								
20	96	Control	..	—	++	++++	++++	++++	Died						

* Infecting dose of trypanosomes, 140,000; single dose of emetin intravenously 24 hours after infection

Few = 1-2 in a field, or in every other field.
+ = about 5-10 in a field.
++ = about 10-20 in a field.
+++ = large numbers that may be roughly counted (not accurately).
++++ = very large numbers; cannot be counted.

TABLE 8

Action of Emetin Hydrochlorid in Vivo on T. lewisi *

Rat	Weight (Grams)	Dose of Emetin (Grams)	Equivalent in Grains per 60 K. or 132 lb. Body Weight	Results of Examination of Blood from Tail											
				24 Hr.	48 Hr.	72 Hr.	96 Hr.	5 Da.	6 Da.	7 Da.	8 Da.	9 Da.	10 Da.	11 Da.	12 Da.
1	80	.00102	12	—	—	—	—	—	Died						
2	99	.00108	10	—	—	—	—	Few	Few	+	++	+++	+++	+++	+++
3	90	.000769	8	—	—	—	Few	Few	+	++	++	+++	++++	++++	++++
4	84	.000539	6	—	—	—	—	Few	Few	+	+	+	++	++	++
5	92	.000411	4	—	Few	Few	Few	Few	+	++	+++	+++	++++	++++	++++
6	92	.000205	2	—	—	—	Few	Few	+	+	++	++	+++	+++	+++
7	77	.000164	2	—	—	—	Few	Few	+	+	++	++	+++	++++	++++
8	70	.000075	1	—	—	—	—	Few	+	++	++	++	+++	+++	+++
9	66	Control	..	—	—	—	Few	Few	+	++	++	++++	++++	++++	++++
10	88	Control	..	—	—	—	Few	+	++	+++	++++	++++	++++	++++	++++
11	90	Control	..	—	Few	Few	+	++	+++	++++	++++	++++	++++	++++	++++
12	80	Control	..	—	—	Few	+	++	+++	++++	++++	++++	++++	++++	++++

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* Infecting dose of trypanosomes, 150,000; single dose of emetin intravenously 24 hours after infection.

(¼ to 1 grain) each day for from 3 to 6 days represents a very high dilution of the drug in the body fluids of the patient, it is readily understood that emetin wields a very high and specific amebacidal action in vivo.

Similar results have been noted in the treatment of amebic dysentery and its complications, the success of the drug in the treatment of this disease having suggested its use in the treatment of amebic pyorrhea.[1]

CONCLUSIONS

Emetin hydrochlorid administered intravenously to rabbits in doses varying from 0.065 to 0.52 gm. (1 to 8 grains) per 132 pounds of body-weight exerted slight or no antiseptic or germicidal influence on a virulent culture of Staphylococcus aureus; abscesses developed in the internal organs of the majority of experimental animals.

Emetin hydrochlorid administered intraperitoneally to mice in doses varying from 0.065 to 0.52 gm. and 0.975 gm. (1 to 8 and 15 grains) per 132 pounds of body-weight exerted no appreciable inhibitory or germicidal action on anthrax and tetanus bacilli.

Emetin hydrochlorid administered intravenously to white rats, infected 24 hours previously by intraperitoneal injection with T. equiperdum and T. lewisi, in doses varying from 0.065 to 0.78 gm. (1 to 12 grains) per 132 pounds of body-weight, appeared to exert a slight trypanocidal influence, which was most apparent in the experiments with T. equiperdum.

Emetin hydrochlorid is highly and specifically amebacidal in vivo, and its curative effects in amebic infections is to be attributed practically solely to this action. While the drug has slight bactericidal powers in vitro under the conditions of prolonged contact with micro-organisms, and while this germicidal action may enhance the value of emetin in the treatment of amebic infections by local application, in the light of our experiments this bactericidal action is not in evidence in vivo.

These observations constitute additional evidence of the active rôle played by Endamoeba gingivalis, Gros, in the pathogenesis of pyorrhea alveolaris; improvement or cure of this disease with emetin by subcutaneous injection is to be attributed solely to its amebacidal action. In the treatment with local applications of the drug the beneficial results are to be ascribed in most part to this same influence, altho here there is reason to believe that the beneficial effects are, to some degree at least, due to a coincident bactericidal influence on the part of the drug.